

5 DEFIBRILLATION ELECTRODE HAVING DRUG DELIVERY
CAPABILITY

 The present invention relates generally to
electrotherapy devices of the type known as "external
10 defibrillators." More specifically, the present
invention relates to an external defibrillator having
patch electrodes which create an electrical pathway for
delivering a defibrillation shock and facilitate the
delivery of drugs into the patient's bloodstream
15 without the use of needles.

 Resuscitation from sudden cardiac arrest (SCA)
often requires the use of various pharmaceutical
agents, such as epinephrine and lidocaine, in order to
improve perfusion and contractile state, stimulate
20 spontaneous contraction and regulate dysrhythmias.
Current research also suggests that pre - and/or post -
defibrillation drug "cocktails" may help protect the
cardiac cells from ischemia and reperfusion related
injury. Unfortunately, these techniques currently
25 require intravenous or endotracheal access, and are
limited to use by advanced life support practitioners.

5 The transdermal applications of drugs is well
established, including over-the-counter products for
the suppression of smoking urges (known as the
"nicotine patch") and the treatment of seasickness.
Transdermal patches offer a method of drug
10 administration which is easily mastered by people
without medical training. Unfortunately, the skin's
poor permeability prevents the timely delivery of most
drugs at therapeutic levels that would be useful for
emergency resuscitation.

15 It is well known that the transdermal delivery of
ionized drugs can be accelerated several hundred
percent via iontophoresis, which is the application of
a small electric potential (typically less than 30
volts) across the medicated patch/skin barrier.

20 Recently, research has been done with pulses of higher
voltage (30 to several hundred volts with a duration of
one to several hundred milliseconds) in a process known
as electroporation. In electroporation, the higher
voltage pulses establish large aqueous pathways for the
25 transfer of macromolecules at therapeutically relevant
rates, demonstrating a drug flux enhancement of up to

5 four orders of magnitude. Electroporation may in turn
be enhanced by the subsequent application of
iontophoretic level voltages. Unfortunately,
electrically enhanced transdermal delivery of drugs
requires the use of specialized electrical equipment in
10 addition to the medicated patches.

A class of portable, external defibrillators has
evolved from the recognition that laypersons or lightly
to moderately trained personnel are at times the first
to administer potentially lifesaving first aid. One
15 such defibrillator is described in U.S. Patent No.
5,607,454 ("the '454 patent"), assigned to Heartstream,
Inc., in which a defibrillator weights a total of less
than four pounds and has a volume of less than 150
cubic inches. This electrotherapy device includes a
20 power source and two electrodes that make electrical
contact with the patient. A premium is placed on
making the device as simple as possible to facilitate
rapid operation while minimizing the risk of accidental
shock.

25 Preferably, the electrodes used in devices of the
type shown in the '454 patent are quickly and easily

5 positioned and attached to the patient. Several particularly advantageous electrode structures for accomplishing these goals have been developed, such as those shown in U.S. Patent No. 5,466,244 ("the '244 patent"), assigned to Heartstream, Inc. FIG. 1 of the
10 present disclosure illustrates a portable defibrillator 10 with two electrodes 12 and 14 properly positioned and attached to a patient. The electrodes of the type shown in the present disclosure include a flexible substrate 16 which is made of polymeric, non-conductive
15 material such as polyester. An electrically conductive metallic foil 18, made of a suitable material such as tin, is located on one surface of the substrate 16, and is electrically connected to control circuitry of the defibrillator 10. An electrically conductive gel layer
20 20 has an adhesive property that permits direct connection to the patient without having to separately tape or otherwise secure the electrodes to the patient. A protective covering (not shown) is typically provided over the patient-contacting surface of the gel layer 20
25 to prevent drying out and to facilitate storage.

5 A need exists to make pharmaceutical intervention available in a more accessible manner, by use of machine automation that in turn makes important treatment available to less trained rescuers and, consequently, a broader population of SCA victims.

10 The present invention is directed to a defibrillator with systems for performing the electrically enhanced transdermal delivery of drugs. The delivery system includes electrically connected medication patches which may be separate from, or
15 incorporated into, the defibrillation electrodes.

 The electrical connection to the medicated patch may be separate from, or coincident with, the defibrillation patch. The defibrillation patches may be used to apply an electric potential across the
20 medicated patch in either a multi-patch electrode or a separate electrode. The defibrillator may also synchronize electrical pulses for the enhancement of drug delivery to features of the patient's ECG so as to minimize the possibility of electrically inducing a
25 cardiac arrhythmia. In one particular embodiment of the invention, the defibrillator may incorporate an

5 algorithm which makes use of a patient -dependent
parameter such as characteristics of the ECG, to
provide guidance to a rescuer, or to automate the
administration of drugs via electrical activation of
the medicated patch.

10 One aspect of the invention is to provide an
apparatus that provides the dual functions of providing
defibrillation and drug delivery. The apparatus
includes a power source, at least one defibrillator
electrode connectable to a subject and being
15 electrically coupled to the power source to receive
electric energy sufficient to defibrillate the subject,
and a drug delivery electrode connectable to the
subject and being electrically coupled to the power
source to receive electric energy sufficient to
20 deliver a drug to the subject.

 In another aspect of the invention, a therapeutic
agent, or drug, is incorporated into the gel layer that
is typically used to attach a defibrillation electrode
to the subject. Thus, a conventional defibrillation
25 electrode of the type that has a conductive layer or
metal foil and a gel layer covering the conductive

5 layer is modified by dispersing a therapeutic agent
into the gel layer. When the drug is incorporated into
the gel layer the circuitry, power supply and/or
programming of the base unit can be modified so that a
drug delivery voltage, or electric energy, is applied
10 to the electrode before, during and/or after
application of the defibrillation voltage or electrical
energy is applied. Such modifications can be hard
wired into the control circuitry, or can be programmed
into a microprocessor, controller or other suitable
15 processing means.

In the disclosed embodiments the control circuit
is constructed to minimize user intervention so that,
for example, the operator can simply attach the
electrodes to the subject and switch on the
20 defibrillator. Operating procedures can be simplified
according to any of the control and operation
procedures of any known variety.

A further variation of the invention involves use
of a single electrode structure to carry electrically
25 isolated regions, each being supplied with a different
electric energy level, such that the higher energy

5 level is applied to the defibrillation region and the lower energy level is applied to the drug delivery region. This embodiment requires coupling each to a different source of energy, or to a different power distribution circuit. For example, to impart the
10 different energy levels, the apparatus may include a primary power supply for supplying defibrillation energy to the defibrillation electrodes and secondary power supply for supplying drug delivery energy to the drug delivery electrode. The secondary supply may be
15 coupled between one of the defibrillation electrodes and the drug delivery electrode.

Further aspects of the invention will become more apparent from the following detailed description when taken in conjunction with the illustrative embodiments
20 in the accompanying drawings.

In the drawings:

FIG. 1 is a schematic view of a defibrillation apparatus known in the art;

FIG. 2 is an enlarged, partial cross-sectional
25 view of one of the electrodes shown in FIG. 1, taken along line 11-11;

5 FIG. 3 is a cross-sectional view similar to FIG. 2, showing an embodiment of the invention in which an electrode has a conductor having a defibrillation portion electrically isolated from a drug delivery portion;

10 FIG. 4 is a top view showing a defibrillation electrode according to another embodiment of the invention, in which drug delivery sections are provided with separate leads for coupling separately to a power source;

15 FIG. 5 is a schematic view of a defibrillation apparatus according to the present invention showing two defibrillation electrodes, either of which could be used to carry a therapeutic agent in its gel layer, or in separate, electrically isolated regions of the gel layer;

 FIG. 6 is a schematic view of the circuitry for the apparatus of FIG. 5;

 FIG. 7 is a schematic view of a defibrillation apparatus according to another embodiment of the invention in which a separate drug delivery electrode is provided;

5 FIG. 8 is a schematic view of the circuitry for the apparatus of FIG. 7; and

 FIG. 9 is a flow diagram showing the process for operating the apparatus.

 The present invention combines a defibrillator
10 electrode incorporating or used in conjunction with a transdermal drug delivery system. Drug delivery can be enhanced using electro-motive forces which can be established and controlled by the control circuitry of the defibrillator. Electro-motive enhancements
15 include, but are not limited to, electro-osmosis and iontophoresis. Preconditioning includes, but is not limited to, electroporation. An advantage to the present invention is that the existing electrode structures need little modification to be adapted for
20 drug delivery.

 An example can be illustrated with reference to FIG. 2, which has been used to illustrate the prior art electrodes. The gel layer 20 can be modified to include an active therapeutic agent within the gel
25 material. In such applications, the structure would not appear physically different from the prior art,

5 although the gel layer would be modified to include the active therapeutic agent.

 Thus, a defibrillation electrode 15 according to the present invention is configured for attachment to a subject, such as someone undergoing a cardiac event.

10 The electrode includes a flexible substrate 16 and a conductive member 18 having an outer surface that would face the subject. The conductive member 18 could be a metal foil, as is used in some prior art devices. A gel layer 20 covers at least a portion of the outer

15 surface of the conductor 18, as in prior art devices, to aid in attaching the electrode to the skin of the subject and establishing a good electrical contact.

 The gel 20 includes a therapeutic agent dispersed within at least a portion thereof in an amount

20 sufficient to establish a desired dosage. The therapeutic agent transports to the subject under the influence of an electromotive force applied through the conductive member.

 The defibrillator circuitry is programmed to

25 operate in an additional mode, called the "electro - motive" mode, in which an electric potential can be

5 established between the electrodes that causes the active agent to migrate from the gel into the bloodstream of the patient through the skin. Iontophoresis provides an electrical driving force to move charged molecules into the subject's skin and thus
10 into the bloodstream. Electroporation, which may also be a desired electro-motive force, involves application of electric field pulses that create transient aqueous pathways in lipid bilayer membranes, causing a temporary alteration of skin structure. The actual
15 transport of charged molecules during pulsing occurs predominantly by electro-osmosis and iontophoresis.

The precise voltages, pulse rates, and nature of the electric field (a.c. vs. DC) can be selected depending on the type of active agent being
20 administered, as well as the dosages. An a.c. voltage will generally not be desirable as an electromotive force but could be used for electroporation.

In keeping with the general goal of providing a defibrillator that is easily operated by the unskilled
25 or layperson, the control circuitry can provide a defibrillation voltage to the electrode 15 as well as a

5 drug delivery voltage. Preferably, the control unit or
base unit includes simple operation switches so that
the drug delivery function is provided automatically,
such as by applying the drug delivery voltage for
predetermined times and durations, such as before,
10 during and/or after application of the defibrillation
voltage.

A microprocessor or microcontroller within the
control circuitry is programmed to automatically
perform electroporation, electromotive drug delivery
15 and/or defibrillation in a pre-determined sequence.
The sequence of these therapies may also be adapted to
a particular patient according to a patient-dependent
parameter. The voltages and/or current necessary to
perform both drug delivery and defibrillation shock can
20 be predetermined or can be selected by the
microprocessor in a look-up table, once the type of
drug is determined either by an automated algorithm or
by manual selection. A user can manually select a drug
type by dial, push-button or by other suitable means.

25 The types of drugs to be administered can be a
variety of cardiac drugs, and virtually any

5 pharmaceutically active agent that might be indicated
for treatment of ventricular fibrillation. One example
of a cardiac drug is a heart stimulant such as
epinephrine. Epinephrine is an endogenous
catecholamine with potent α - and β -adrenergic
10 stimulating properties. In cardiac arrest, α -
adrenergic-mediated vasoconstriction is the most
important pharmacologic action because restoration of
aortic diastolic pressure is a critical determinant of
success or failure of resuscitation. Vasoconstriction
15 elevates perfusion pressure, thus enhancing delivery of
oxygen to the heart. Other cardiac drugs that could be
delivered using the present invention include
adenosine, bretylium, atropine sulfate, and lidocaine.
Lidocaine is used to suppress ventricular ectopy and to
20 raise the threshold for ventricular fibrillation.

FIG. 3 illustrates an alternative embodiment of a
defibrillation electrode 22 which is attachable to a
subject as in the previous embodiment. An electrically
non-conductive substrate 24 has opposite surfaces, one
25 of which is connected to a first conductive member 26
having an outer surface, and a second conductive member

5 28 having an outer surface. The first and second
conductive members 26 and 28 are electrically isolated
from each other, or substantially isolated from each
other, by insulator 30.

A first gel layer 32 is connected to at least a
10 portion of the outer surface of the first conductive
member 26, and a second gel layer 34 is connected to
at least a portion of the second conductive member 28.
As illustrated, the insulator 30 also electrically
isolates the first gel layer 32 from the second gel
15 layer 34, although an air gap may also provide
sufficient isolation. In this embodiment the
therapeutic agent is dispersed within at least a
portion of the second gel layer 34, so that the
therapeutic agent transports to the subject under the
20 influence of an electro-motive force applied through
the second conductive member 28.

The electrical isolation provided herein allows
for the power source, or multiple power sources, to
provide electric energy to the different conductive
25 members at different levels, at different times, and
for different purposes. Thus, conductive member 26

5 could be connected to a first power source, and
conductive member 28 connected to a second, different
power source. Alternatively, they could be connected
through different circuitry and/or switch combinations
to provide different levels of energy from the same
10 power source at the same or at different times.

 The second gel layer 34 may consist of areas
containing different drugs and/or additional doses of a
drug. Optionally, different defibrillation electrodes
can be provided with different drugs and different
15 doses of drugs, and may thus be preconnected to a
particular defibrillation device or may be connectable
to the device with instructions as to which of the
different drug-carrying electrodes to use. It is
recognized, however, that in most cases user
20 intervention is to be simplified, so that preferred
embodiments would require no user selection of
electrodes.

 According to another embodiment of the present
invention multiple therapeutic drug "patches" can be
25 provided on a single electrode, for the purpose of
providing additional dosage of a single drug, or for

5 simultaneously administering two drugs. Referring to
FIG. 4, a defibrillation electrode 36 has a non -
conductive substrate 38 which carries three different
conductors: a first one corresponding to the larger
diameter circle, and second and third ones
10 corresponding to the smaller diameter circles. Each
conductor is electrically isolated from the other. A
first gel layer 40 covers the first conductor while gel
layers 42 and 44 cover the second and third conductors,
respectively. The area around each of the gel layers
15 42 and 44 represents insulator material or a gap which
electrically insulates the gel layers 42 and 44 from
the gel layer 40.

As shown in FIG. 4, each of the conductors is
connected to a separate electrical lead, such as leads
20 46, 48, and 50, so that a different and separate amount
of electric energy can be applied to each. For
example, a defibrillation voltage can be applied to the
first electrode, while no voltages are applied to the
second and third electrodes, and drug delivery voltages
25 can be applied to the second and third electrodes while
no voltage is applied to the first electrode. Timing,

5 sequence, duration and levels of applied electric energy can be determined by the control circuits of the defibrillator.

Referring to FIG. 5, a defibrillation apparatus 52 includes a base unit 54 and a pair of defibrillation electrodes 56 and 58. In most respects, the apparatus 52 corresponds to a type of device known as automated external defibrillators ("AED's"), which are highly portable and designed to be used by laypersons or otherwise by those who are unskilled in the medical arts. Operation is automated to the greatest extent possible, so that the operator can simply attach the electrodes and turn the device on and most every other function that follows is performed automatically by automated diagnosis and/or pre-programming.

20 The base unit 54 includes a power supply (not shown in Fig. 5) and a control circuit which makes delivery of a defibrillation shock to a subject via the electrodes 56 and 58. The electrodes are easily attached to the subject's skin prior to initiation of the defibrillation shock. The power supply and control circuitry for establishing a defibrillation shock are

5 known and described in other patents assigned to
Heartstream, Inc..

In order to induce drug delivery through the
defibrillation electrodes one of the electrodes 56 or
58 is provided with a therapeutic agent in the gel
10 layer so that, when an appropriate electro-motive force
is applied, the therapeutic agent transports across the
skin from the gel layer and into the bloodstream of the
subject.

As noted above, the electrodes may carry the
15 therapeutic agent on the same electric circuit, or on
electrically isolated circuits, and preferably the
latter. Isolated circuits will allow the
administration of a drug or drugs independently of the
defibrillation circuit.

20 As seen in FIG. 6, the base unit 54 includes a DC
power supply 60 which is the source of energy for
imparting defibrillation and drug delivery. A control
circuit 62 may be hard-wired to provide both
defibrillation energy and drug delivery energy at
25 specified times and sequences once the operator
activates the apparatus, for example, by pushing an

5 "on" button 64. A separate button or switch 65 may be provided to enable the operator to initiate drug delivery. For example, in the instructions provided with the apparatus, the operator may be told to push the drug delivery button 65 after delivery of a
10 defibrillation shock. In the absence of a drug delivery button, the apparatus may include programming or circuitry that automatically initiates drug delivery through the drug delivery circuit.

FIG. 7 illustrates an embodiment in which the
15 defibrillation apparatus 66 includes a base unit 68, two defibrillation electrodes 70 and 72, and a drug delivery electrode 74. In appearance, the electrode 74 can resemble the defibrillation electrodes in having a non-conductive substrate, a conductive layer, and a gel
20 layer, with the distinction being that the gel layer will include a therapeutic agent. Also, the amount of electric energy supplied to the drug delivery electrode will be of a smaller magnitude; voltages, pulse rates and durations can be selected to optimize delivery of a
25 particular drug. As with the other electrodes, the drug delivery electrode 74 is attached to the skin of

5 the subject for whom a defibrillation procedure is
being initiated.

In the embodiment of FIG. 7, the drug delivery
electrode 74 may be coupled to a separate power source.
Referring to FIG. 8, the base unit 68 may include a
10 first power supply 76 for providing electric energy to
the defibrillation electrodes and a second power supply
78 for providing electric energy to the drug delivery
electrode 74 at levels and for times sufficient to
impart drug delivery. The power supply 78 may be
15 connected between the drug delivery electrode 74 and
one of the defibrillation electrodes as shown in FIG.
8.

The control circuit 80 can be programmed or wired
to switch the different power supplies on and off at
20 preferred times and durations. Also, the control
circuit may include means for adjusting the power
output to the electrodes depending on subject-dependent
parameters.

Operation of the defibrillator to accomplish both
25 the defibrillation function and the drug delivery
function can either be automatic, manual, or a

5 combination of both. In the various embodiments described herein, the control circuit may include a microprocessor or any other integrated circuit means which includes or is coupled to a memory for storing electrical parameters for operation of the apparatus in
10 a defibrillation mode and a drug delivery mode. Moreover, multiple parameters can be stored, corresponding to multiple types of drugs, for use in the drug delivery mode, and multiple parameters can be stored for operation at different levels in the
15 defibrillation mode. The selection of electrical parameters for drug delivery is dependent on the type and dosage of drug as well as the desired rate of delivery. Thus, these values can be stored in a look-up table as part of the programming of the
20 microprocessor or permanently stored in ROM (read-only memory).

It is further possible to monitor the heart condition of the patient through an additional sensor and electrical lead or by using the electrodes and
25 their electrical leads so that the control circuit can indicate to the user the times to defibrillate or to

5 deliver medication. Preferably, the drugs are
incorporated into the electrodes and are electrically
isolated so that each can be delivered separately, if
multiple drugs are provided, and if multiple doses are
used. In some instances only drug delivery may be
10 called for. At other times there may not be time or
the desirability for drug delivery and the
defibrillation mode is immediately selected. After
defibrillation, drug delivery may then be selected
manually or automatically. In any event, selection of
15 the drug delivery mode can be manual, meaning by user
selection, or automatic, meaning following execution of
a software routine, based simply on timing or based on
a comparison of sensed heart parameters to stored heart
parameters.

20 A simple flow chart indicating how to program the
unit is shown in FIG. 9. The first step 82 is
"monitor," in which sensors connected to a person who
might be experiencing a cardiac event produce signals
indicative of the condition which are fed into a memory
25 device, such as a RAM or other suitable device, for
comparison to stored values. As a result of this

5 comparison a visual display may prompt the operator to
initiate defibrillation by actuating an "on" switch.
This is indicated by the step 84 for "defibrillate," in
which a defibrillator voltage is applied to the
electrodes for a predetermined time and at a
10 predetermined level. Defibrillation may occur by
automatic program execution, thus eliminating the need
for an operator to push the "on" button. Drug delivery
may be desirable prior to providing a defibrillation
shock.

15 Following defibrillation, the program may provide
a drug delivery step 86 in which the drug delivery
electrode is powered to impart transdermal drug
delivery. The base unit may be provided with a display
which, after a predetermined time after defibrillation,
20 tells the operator to turn on the drug delivery
electrode. This would require a second button or
switch on the base unit, such as button 65 shown in
FIG. 6. When the button 65 is pushed, the control
circuit delivers a voltage to the drug delivery
25 electrode for a predetermined time and at a
predetermined energy level. Optionally, the control

5 circuit may include a timer so that drug delivery is initiated automatically after defibrillation, thus minimizing operator interaction.

“Monitoring” can occur manually, such as by a user checking the pulse, checking breathing, etc., to
10 determine the condition of a person who might be experiencing a cardiac event; in the event of manual checking, the software routine need not include a monitoring step. If monitoring is done manually, the “defibrillate” step is done manually by user
15 manipulation of a switch. If drug delivery mode is selected, either manually or automatically, the system can be programmed to automatically select a drug or multiple drugs and the dosage, if the apparatus is provided with multiple, electrically isolated drug
20 patches or drug delivery electrodes (which may be incorporated on a single electrode).

The program sets the electrical parameters, optionally to provide for electroporation to reduce the skin barrier to transdermal medication flux, prior to
25 initiating electro-osmosis. Thus, the program can establish the electric potentials required to provide

5 electroporation prior to drug delivery and electro -
osmosis during drug delivery. These potentials provide
an electro-motive force of sufficient strength to
transport drugs into the bloodstream of the person
undergoing a cardiac event at a desired dosage and
10 rate. When the electrodes are coupled to the power
source, preferably a DC power supply, the program or
circuitry of the apparatus provides voltage and/or
current levels sufficient to accomplish electroporation
(optionally) followed by the delivery dosage and rate.

15 In the defibrillation mode, electrical parameters
are preferably set automatically and the electrodes are
coupled to the power supply to deliver the
defibrillation shock. The general operation of the
defibrillator in this mode is well understood from
20 various patent to Heartstream, In., including the
aforementioned U.S. Patents Nos. 5,607,454 and
5,466,244, which are hereby incorporated by reference.

In the simplest implementation of the present
invention, the drugs are prepackaged in the electrodes,
25 and no selection process is required; the user simply
attaches the electrodes to the person undergoing a

5 cardiac event. Usually, no drug delivery is desired
before defibrillation, although the device may be
programmed to do so. This is true only because
administering drugs delays defibrillation. It may be
preferable to deliver drugs first via automation if
10 defibrillation is not delayed. Preferably, immediately
after defibrillation, a DC current of sufficient
duration and magnitude is supplied to the drug delivery
electrode or portion of an electrode to cause release
of the drugs and their transfer across the skin
15 interface and into the circulatory system.

The circuitry described above may be designed or
controlled by a programmed microprocessor to deliver a
voltage at levels and for times sufficient to deliver
drugs from one or more transdermal patches. The
20 patches may be separate from the shock delivering
electrodes of the defibrillator, or may be coincident
with the defibrillation electrodes. In any event, the
drug delivery voltages can be pulsed at high or low
voltages. For high voltages the voltage values can
25 range from 30 to 2500 volts, for durations of between
0.5 milliseconds and 5 seconds. The voltage is

5 delivered through electrode patches that carry the drug
for the purpose of electrically enhancing the
transdermal administration of the medication, and more
specifically for electroporation of the stratum
corneum.

10 For lower voltages, the voltages are pulsed
between 0 and 50 volts for durations between 0.1 second
and thirty minutes. The voltage is delivered through
electrode patches that carry the drug for the purpose
of electrically enhancing the transdermal
15 administration of the medication, and more
specifically, for iontophoretic assistance of transport
for ionic medications. Other voltages and durations,
as well as other transport phenomena, can be used.

Reference herein to a "gel" is a reference to a
20 preferred carrier for the drug, in that AED's are
currently available that use gel adhesive layers to
attach the defibrillation pads or electrodes to the
subject. The term "carrier" is used to indicate that
the therapeutic agent or drug is carrier by another
25 substance, which could be the material that forms the
gel layer of known defibrillation electrodes, or it

5 could encompass other media, such as paste or creams
which have little or no adhesive characteristic.
Although it is conceivable that the drug could be
applied to the skin separately from the electrode
structure, this might require more operator
10 intervention than is desired, and thus such drug
applications would be less preferred.